UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/824,980	04/15/2004	Nolan James Dewdney	R0164B-REG	7688

24372 7590 09/18/2006

ROCHE PALO ALTO LLC
PATENT LAW DEPT. M/S A2-250
3431 HILLVIEW AVENUE
PALO ALTO, CA 94304

EXAMINER	
JAISLE, CECILIA M	

ART UNIT	PAPER NUMBER
1624	

DATE MAILED: 09/18/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/824,980	DEWDNEY ET AL.	
	Examiner	Art Unit	
	Cecilia M. Jaisle	1624	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *15 April 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *15 April 2004*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claim Rejections – 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-22 are based on a specification that, while being enabling for making pharmaceutically-acceptable salts of the claimed compounds, does not reasonably provide enablement for isomers and prodrugs of the claimed compounds. The specification discusses isomers at page 12, *inter alia,* and prodrugs at page 11, *inter alia.*

The specification does not enable one skilled in the art to which the present invention pertains to make all isomers and prodrugs envisioned by the specification commensurate in scope with the claims. There is no description, beyond exemplification of the Formulae (I) and (II) compounds, of the variation in nature or sequence of atom bonding arrangement in other isomeric compounds that may have the same number and identity of atoms. For example, the molecular formula $C_3H_7NO_2$ identifies ten structurally and chemically different compounds (see page FI-8 of the Merck Index) with distinctly different chemical and physical properties. In regard to prodrugs, there is no description, beyond the exemplification of hydroxyl, amino and sulfhydryl groups, of the functional groups to be modified or the modifications, beyond the exemplification of esters and carbamates of hydroxy functional groups. The factors

to be considered in making an enablement rejection have been summarized as a) the quantity of experimentation necessary, b) the amount of direction or guidance presented, c) the presence or absence of working examples, d) the nature of the invention, e) the state of the prior art, f) the relative skill of those in the art, g) the predictability or unpredictability of the art and h) the breadth of the claims. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

a) Determining all compounds encompassed by the molecular formula of a compound of Formulae (I) and (II) would involve synthesizing and *in vivo* testing to confirm that all such isomers have the pharmaceutical properties asserted for the Formulae (I) and (II) compounds. Determining if a particular compound of Formulae (I) and (II) would form a prodrug would require synthesis of the prodrug and *in vivo* testing to determine targeting and regeneration of the parent compound. Bodor, et al., "Chemical Approaches to Drug Delivery," at page 291-2 (in Encyclopedia of Controlled Drug Delivery, 1999, John Wiley & Sons, pages 285-298) states, "In general, prodrugs do not achieve significant drug targeting, which is the major way to improve the therapeutic index of a drug." The experimentation for determination of prodrugs is potentially open-ended.

b) The specification at pages 11-12 simply states Applicants' intent to make isomers and prodrugs, without any definition of the intended metes and bounds thereof.

c) While the claims recite isomers and prodrugs, no working examples show their formation. As stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190, 1194 (CAFC 1993):

> The specification purports to teach, with over fifty examples, the preparation of the claimed compounds ... However ... there is no evidence that such compounds exist ... [T]he examples ... do not produce the postulated compounds ... [T]here is ... no evidence that such compounds even exist.

The same issue appears to be true here; the specification shows no evidence of the formation and actual existence of these derivatives. Hence, Applicants must show formation of isomers and prodrugs or limit the claims accordingly.

d) The nature of the invention is chemical synthesis of isomers and prodrugs, which involves chemical reactions.

e) The state of the art recognizes that the formation, composition and therapeutic activity of isomers and prodrugs are unpredictable. Bodor, discussed *supra*, acknowledges that the activity of prodrugs is empirically determined. The Merck Index, discussed *supra*, recognizes structurally, functionally and chemically different compounds that have the same molecular formula and distinctly different chemical and physical properties.

f) The artisan using Applicants' disclosure to prepare the claimed isomers and prodrugs would be, e.g., an experienced organic chemist with at least a BS chemistry degree.

g) Chemical reactions are well known to be unpredictable. *In re Marzocchi, et al.*, 169 USPQ 367, 370 (CCPA 1971). *In re Fisher*, 166 USPQ 18, 24 (CCPA 1970). The added unpredictability of isomer and prodrug formation is discussed *supra*.

h) The breadth of the claims includes thousands of compounds of the Formulae (I) and (II), as well as presently unknown compounds embraced by the words

isomers and prodrugs. Note MPEP 2164.01(a) and 2164.04 clearly justifying the conclusion of lack of enablement commensurate with the claims. Thus, undue experimentation will be required to practice Applicants' invention.

Claims 18-20 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of treating arthritis, does not reasonably provide enablement for a method of treating a p39-mediated disorder generally; or a method of inhibiting p38 kinase in a mammal generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The specification does not provide reasonable enablement for the breadth of claimed Formulae (I) and (II) compounds for the various p38-mediated disorders, including those yet to be discovered, embraced by claims 18-20. Lee, et al., "p38 Mitogen-Activated Protein Kinase Inhibitors – Mechanisms and Therapeutic Potentials," Pharmacol. Ther., 1999 May-June; 82(2-3): 389-97, teaches p38 MAPK inhibitors are efficacious in arthritis disease models. Accordingly, Lee establishes enablement for the compounds of claimed Formulae (I) and (II) for methods of treating or inhibiting arthritis. The following reasons apply to the present enablement rejection.

The scope of independent claims 18 and 20 includes not only the recited disorders but also those disorders/conditions yet to be discovered as associated with p-38 protein kinase inhibitory activity for which there is no enabling disclosure. The scope of claim 19 includes recited disorders for which the specification provides no correlation

between *in vitro* p-38 protein kinase inhibitory activity and successful therapeutic treatment of those diseases/conditions. In addition, the scope of these claims includes treatment of various disorders/diseases, which are not adequately enabled solely based on *in vitro* p-38 protein kinase inhibitory activity (pages 26-30). The claimed compounds are disclosed to demonstrate *in vitro* p-38 kinase inhibitory activity and the specification recites that the claimed compounds are therefore useful to treat all diseases caused or exacerbated by p-38 MAP kinase activity, for which the record provides no competent correlation evidence. Furthermore, the record has not provided competent evidence that the instantly disclosed tests (pages 26-30) are highly predictive for all the uses disclosed and embraced by the claim language for the intended host. Lee teaches 'p38 MAPK inhibitors are efficacious in arthritis disease models.'

Moreover, many if not most diseases said to be controlled by the claimed compounds, such as Alzheimer's disease, adult respiratory distress syndrome, stroke, etc., are known to be difficult to treat and at present no known drug can successfully reverse the course of these diseases, despite the fact that many drugs are said to demonstrate *in vitro* p-38 kinase inhibitory activity. Substantiation of utility and its scope is required when utility is "speculative," "sufficiently unusual" or not provided. See *Ex parte Jovanovics, et al.*, 211 USPQ 907, 909 (BPAI 1981). Also, note *Hoffman v. Klaus*, 9 USPQ2d 1657 (BPAI 1988) and *Ex parte Powers*, 220 USPQ 924 (BPAI 1982) regarding types of testing needed to support *in vivo* uses.

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999), emphasizing

Applicants' attention is drawn to the Revised Interim Utility and Written Description Guidelines, at 64 FR 71427 and 71440 (December 21, 1999), emphasizing that "a claimed invention must have a specific and substantial utility." See also MPEP 2163, *et. seq.* The disclosure in the instant case is not sufficient to enable the instantly claimed method of treating based solely on *in vitro* p-38 kinase inhibitory activity. The state of the art is indicative of the requirement for undue experimentation. Hashimoto, et al. ("Selective Inhibitor of p38 Mitogen-Activated Protein Kinase Inhibits Lipopolysaccharide-Induced Interleukin-8 Expression in Human Pulmonary Vascular Endothelial Cells," Journal of Pharmacology and Experimental Therapeutics, Vol. 293, No. 2, pp. 370-375, 2000) studied SB 203580, a pyridinyl imidazole selective inhibitor of p38 MAP kinase activity in relation to potential therapeutics for ARDS (adult respiratory distress syndrome), and concluded the need for further investigations, because the authors could not determine if SB 203580 is capable of producing beneficial effects on ARDS. Hensley, et al. ("p38 Kinase Is Activated in the Alzheimer's Disease Brain," Journal of Neurochemistry, Vol. No. 5, 1999, pp. 2053-2058), in studies on the AD (Alzheimer's disease) brain, observed that "... phosphorylation has not been characterized *in vivo* in diseased human tissue, and few data regarding p38 have been obtained from mammalian brain..." concluding that "Further investigation is warranted to understand the mechanisms by which p38 phosphorylation is regulated and dysregulated in AD and other chronic inflammatory conditions." Johnson, et al. ("Mitogen-Activated Protein Kinase Pathways Mediated by ERK, JNK, and p38 Protein Kinases," Science, Vol. 298, 6 Dec. 2002, 1911-1912) noted p38 pathways as

molecular targets for drug development, and suggested MAPKs as a drug group for potential development in human disease therapy. Blease ("Targeting Kinases in Asthma," Expert Opin. Investig. Drugs, 2005, Vol. 14, No. 10, 1213-1220) observed that, due to apparent toxicity issues, p38 inhibitor clinical trials are moving relatively slowly and that "research into the potential for targeting kinases towards the treatment of asthma has only just begun." All of this information indicates the need for undue experimentation to establish enablement for the present claims.

Many factors require consideration when determining whether sufficient evidence supports a conclusion that a disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue." MPEP 2164.01(a). These factors include: (1) the breadth of the claims; (2) the nature of the invention; (3) the state of the prior art; (4) the level of predictability in the art; (5) the amount of direction the inventor provides; (6) the presence of working examples; and (7) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)(reversing the PTO's determination that claims directed to methods for detection of hepatitis B surface antigens did not satisfy the enablement requirement). See also *In re Goodman* 29 USPQ2d 2010, 2013 (CAFC 1993). Application of these factors to the present application supports the determination that the present disclosure fails to satisfy the enablement requirement:

1. Breadth of the claims: The instant claims embrace all conditions, including those yet to be determined, related to p-38 kinase activity.

2. Nature of the invention: Therapeutic use of the claimed compounds in treating diseases/conditions caused or exacerbated by p-38 kinase activity.

3. State of the prior art: See the discussions *supra* of Hashimoto, Hensley, Johnson and Blease, as contrasted with Lee.

4. Level of predictability in the art: Applicants do not provide highly predictive competent evidence or recognized tests for treating all conditions recited for the claimed compounds. Pharmacological activity in general is very unpredictable. In applications involving physiological activity, such as the present,

> "The first paragraph of 35 U.S.C. §112 effectively requires that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art."

Plant Genetic Systems N.V. v. DeKalb Genetics Corp., 65 USPQ2d 1452, 1456 (CAFC 2003).

5. Amount of direction provided; and (6) presence of working examples: The specification working examples do not show treatment of all conditions. The state of the art (e.g., Hashimoto, Hensley, Johnson and Blease, as opposed to Lee) supports that successful treatment of conditions caused or exacerbated by p-38 kinase activity is unpredictable and, at best, limited to *in vitro* inhibition of p-38 kinase activity.

7. Quantity of experimentation needed to make or use the invention: Based on the content of the disclosure, the quantity of experimentation needed would place an undue burden on one skilled in the pharmaceutical arts, since the disclosure

gives the skilled artisan inadequate guidance regarding pharmaceutical use, for the reasons stated above.

Consideration of the above factors demonstrates that the present application lacks sufficient enablement of the present claims. In view of the claim breath, the pharmaceutical nature of the invention, the unpredictability of relationship between *in vitro* inhibition of p-38 kinase activity and alleviation of specific diseases/conditions, one of ordinary skill in this art would have to undergo an undue amount of experimentation to use the instantly claimed invention commensurate with the claim scope.

The Supreme Court has recognized that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion." *Brenner v. Manson*, 148 USPQ 689, 696 (U.S. 1966). See also *In re Genentech, Inc. v. Novo Nordisk A/S*, 42 USPQ2d 1001, 1005 (CAFC 1997)("patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable.")

MPEP 2164.01(a) states,

> A conclusion of lack of enablement means that, based on the evidence regarding each of the above [Wand] factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 27 USPQ2d 1510, 1513 (CAFC 1993).

The above consideration clearly justifies that conclusion here and undue experimentation would be required to practice Applicants' invention, other than as specifically noted above.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1-22 are rejected under 35 USC 112, paragraph 2, for failing to particularly point out and distinctly claim the subject matter that the Applicants regard as their invention. The term "isomers" include all isomeric form types, including positional isomers, which are neither supported in the specification nor shown by examples. The specification at page 13, lines 10-21 provides explanation regarding "stereoisiomers," however, the term "isomers" includes structural isomers, positional isomers, and all other isomeric forms. As the structural Formulae (I) and (II) show the substituents at specific positions, it is not clear what is intended by the recitation of "an isomer thereof."

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Cecilia M. Jaisle, J.D. whose telephone number is 571-272-9931. The examiner can normally be reached on Monday through Friday; 8:30 am through 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James O. Wilson can be reached on 571-272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Cecilia M. Jaisle, J.D.

DEEPAK RAO
PRIMARY EXAMINER